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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/008,062	10/19/2001	David Rizzieri	5405-252	5735

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MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/008,062	RIZZIERI ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-21 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-21 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3/7/2002;6/14/004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-21 are pending.

Claims 1-21 are examined on the merits.

Information Disclosure Statement

2. At the time of examination reference 1, RE 38,008 (02/25/2003) cited on the information disclosure statement (IDS) submitted May 8, 2003 was unavailable to the Examiner. This document will be reviewed and duly noted as so in the next response to Applicants.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating lymphoma in a subject comprising administering to said subject a radiolabeled chimeric ^{131}I-81C6, does not reasonably provide enablement for any antibody that binds tenascin, as well as a naked 81C6 antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants' specification has provided evidence that substantiates the administration of the chimeric ^{131}I-81C6 monoclonal antibody resulting in decreased

tumor size, see page 16, lines 1-20; page 17, Table 4; page 22, line 9 to page 32, line 18. The specification does not provide data that demonstrates the effective use of a naked antibody, one in which it is not coupled to a therapeutic agent, such as a toxin, radiolabel or toxin. There is insufficient evidence provided in the specification that an 81C6 antibody devoid of a therapeutic agent would be able capable of inhibiting or arresting cell function, as well as target a cancer cell. In addition a review of the literature provided by Applicants does not reveal the successful implementation of a naked 81C6 antibody in the treatment of any form of cancer. Accordingly, one of ordinary skill in the art would not be able to successful practice the invention according to the broad claims.

5. Claims 4 and 12-21 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of a hybridoma that produces an antibody named 81C6. It is not clear that hybridomas that produce the antibody identified, as 81C6 capable of possessing the identical properties of the 4A4 antibody is known, publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of an antibody is an unpredictable event. Although applicant has

provided a written description of a method for generating and isolating the specified monoclonal antibodies, this method will not necessarily reproduce antibodies and which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive antibodies identical to those claimed. Undue experimentation would be required to screen all of the possible antibody species to obtain the claimed antibody.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the antibody listed in claims 4 and 12 a suitable deposit of the molecules designated as 81C6 for patent purposes, evidence of public availability of the claimed cell lines or evidence of the reproducibility without undue experimentation of the claimed cell lines, is required.

Applicants have not made a referral to the deposit of the antibodies in the specification. There is insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is

necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 5,624,659 (April 29, 1997/ reference 1 from IDS submitted June 14, 2002), and in view of Rizzieri et al. (Blood 94(10), Part 2, Supplement 1: 4339, Abstract #4339 November 1999/ reference 3 from IDS submitted June 14, 2003). U.S. #5,624,659 teaches methods of treating solid and cystic tumors or an organ that expresses tenascin using the radiolabeled chimeric monoclonal antibody, ^{131} I -81C6, see abstract; bridging paragraph of columns 1 and 2; Examples 2-4 and 6 of columns 5-7. In particularity the monoclonal antibody 81C6 is a murine IgG2b that may be coupled to a radioisotope, cytotoxic agent and chemotherapeutic agent, see column 3, lines 13-46. "The dosage of the antibody will depend ...on the tumor being treated, the route of administration, the nature of the therapeutic agent employed, and the sensitivity of the tumor to the particular therapeutic agent.", see column 4, lines 27-44. For example, wherein the therapeutic agent is ^{131} I, the dosage will typically be from 5,000 Rads to 100,000 Rads. The therapeutic 31C6 antibody can be administered intra-arterially or

parenterally via an intravenous injection, see column 4, lines 16-26. U.S. Patent '659 does not teach a method of treating Hodgkin's lymphoma or Non-Hodgkin's lymphoma, wherein the Non-Hodgkin's lymphoma is unresponsive to rituximab treatment and chemotherapy treatment with a 81C6 monoclonal antibody coupled to a radioisotope.

However, Rizzieri does teach that Non-Hodgkin's lymphoma patients have increased expression of tenascin, specifically in lymphomatous tissue. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to treat Hodgkin's lymphoma, as well as Non-Hodgkin's lymphoma patients with varying forms of the disease and unresponsive to chemotherapeutics with the therapeutic monoclonal antibody of patent '659. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the patent that any tumor that expresses tenascin could be treated with the therapeutic 81C6 monoclonal antibody and because the abstract of Rizzieri suggests that "...[Non-Hodgkin's] disease suggests systemically delivered anti-tenascin antibody may be an effective form of therapy.", see patent, column 4, lines 1-3 and last paragraph of abstract. Furthermore, it would have been *prima facie* to one of ordinary skill in the art to implement another mode of therapy to a patient with Non-Hodgkin's lymphoma that was unresponsive to chemotherapy treatment. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Rizzieri, which very clearly teaches that tenascin is found on lymphomatous tissue and delivery of an anti-tenascin antibody may prove to an effective form of treatment.

Conclusion

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Rizzieri et al. Phase I Trial study of ^{131}I-labeled chimeric 81C6 monoclonal antibody for the treatment of patients with non-Hodgkin's lymphoma, Blood, April 20, 2004, [Epub ahead of print].

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571) 272-0831. The examiner works a flexible schedule, but can normally be reached between the hours of 6:30 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christine Y. Chan can be reached on (703) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AMHarris

Alana M. Harris, Ph.D.
28 June 2004
ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER